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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,824	05/27/2005	Kenji Miyazaki	Q88284	1306

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EXAMINER	
XU, XIAOYUN	

ART UNIT	PAPER NUMBER
1797	

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05/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,824	MIYAZAKI ET AL.	
	Examiner	Art Unit	
	ROBERT XU	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,7,12 and 14-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,7,12 and 14-27* is/are rejected.

7)☐ Claim(s) *3, 7, 12, 14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed 03/12/2009 has been entered and fully considered. Claims 1, 2, 4, 6, 8-11 and 13 are canceled. Claims 3, 7, 12 and 14-27 are pending, of which Claims 3, 7, 12 and 14 are amended, Claims 15-27 are new.

2.

Response to Amendment

2. In response to amendment, the examiner establishes objection and maintains rejection over the prior art established in the previous Office action.

Claim Objections

3. Claims 3, 7, 12, and 14 are objected to because of the following informalities: Claims 3, 7, 12, and 14 do not refer to a proceeding claim. Appropriate correction is required.

Claim Rejections - 35 USC § 103

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. **Claims 3, 7, 12 and 14-27** are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsugita et al. (Electrophoresis, 1998) (Tsugita) in view of Tsugita'1992 (Chemistry Letters, 1992) and Vogt et al. (Polymer Bulletin, 1996) (Vogt).

In regard to Claim 15, Tsugita teaches a method for analyzing the C-terminal amino acid sequence of a peptide. The method comprises steps of:

releasing the C-terminal amino acids successively from the peptide by chemical procedure to prepare a mixture containing the original peptide and a series of peptide reaction products (see page 930, right col., 3rd paragraph),

analyzing the original peptide and the series of the peptidyl reaction products produced at the releasing step by means of mass spectrometry to measure the decrease in molecular weight associated with the successive release of the C-terminal amino acid (see page 931, left col. 2nd paragraph), and

identifying a series of the C-terminal amino acids removed successively, based on a series of the measured decrease in molecular weight (see page 931, left col. 2nd paragraph),

Tsugita uses PFPMe in the sub-step (2) in the procedure (see page 930, right col., 3rd paragraph); Tsugita also uses perfluoro-alkanoic acid (PFPA) for cleavage at C-side of aspartic acid and the N-side of serine/threonine and simultaneous successive truncation at the C-termini of the cleaved fragments (see abstract). PFPMe and PFPA have similar structure and functions. Tsugita'1992 teaches using PFPA in the second step of the procedure to successively release N-terminal amino acid (see page 236, flow chart). At the time of the invention, it would have been obvious to ordinary skill in the art to use PFPA in the second step of the procedure based on teaching of Tsugita'1992 and Tsugita.

Tsugita teaches that the releasing step of the procedure needs to be carried out in the absence of water (page 931, right col. 2nd paragraph, last 2 lines; page 930, 3rd paragraph). Therefore, the target protein has to be extracted from the gel and then dried to remove water or electroblotted to an Immobilon-CD membrane.

Tsugita does not teach using dipolar-aprotic solvent to swollen the gel so that the above reaction could be carried out on the protein bound to the original gel right after electrophoresis. Vogt teaches a new non-aqueous swelling system that carboxymethyl cellulose (CMC) gel treated with a dipolar aprotic solvent like *N,N*-dimethylacetamide with *p*-toluenesulfonic acid yields a high reactive gel-suspension of the polymer (see abstract). This dipolar aprotic solvent can remove water from the swollen gel in one step (see page 550, 3rd paragraph), thus allows a direct esterification of the hydroxyl group of CMC (see abstract). At the time of the invention, it would have been obvious to one of ordinary skill in the art to use dipolar aprotic solvent to remove water from the gel carrier bound with the target protein, as taught by Vogt with reasonable expectation that this would allow Tsugita's procedure be carried out on the target protein kept on the gel carrier.

Tsugita teaches that the successive release of C-terminal amino acid results from the reaction process with formation of 5-oxazolone-ring structure (see page 930, right col., 3rd paragraph).

In regard to Claim 16, Tsugita teaches that the concentration of the alkanoic acid anhydride contained in the mixture is 20% by volume (see page 930, right col., 3rd paragraph).

In regard to Claim 17, the temperature of 5° used in the second step of Tsugita's procedure is lower than the 30-80° recited in the instant claim. Applicant is advised that generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, it would have been obvious to one of ordinary skill in the art to discover the optimum range of the reaction temperature by routine experimentation.

In regard to Claims 3, 18 and 19, Tsugita teaches that 20% acetic anhydride is used in the mixture solution for applying N-acetylation protection to the N-terminal of the protein and for forming oxazolone at C-terminal of the protein (page 930, right col. 3rd paragraph). Tsugita in view of Vogt teaches that the process can be done in a dipolar aprotic solvent.

In regard to Claim 20, the pH of PFPA is 0.8.

In regard to Claims 7 and 21, PFPA has 3 carbon atoms linear-chain.

In regard to Claim 22, as has been discussed in regard to Claims 15, in light of teachings of Tsugita and Tsugita'1992, the ratio of PFPA (5%) to acetic anhydride (20%) would be 1:4. In the instant Claim, the lower limit is 20:100 or 1:5. Applicant is advised that generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, it would have been obvious to one of ordinary skill in the art to discover the optimum ratio of perfluoroalkanoic acid to alkanoic acid anhydride by routine experimentation.

In regard to Claim 23, Tsugita teaches that the sub-step (2) of the procedure needs to be carried out in the absence of water (page 931, right col. 2nd paragraph, last 2 lines; page 930, 3rd paragraph). Tsugita'1992 teaches that the target peptide is dried in a small test tube. The tube is placed in a large test tube which contained PFPA in acetonitrile (page 235, last paragraph). The

large tube is flame sealed under vacuum. This implies that the reaction is carried out in the test tube where oxygen has been eliminated.

In regard to Claims 14 and 24, Tsugita teaches that the sub-step (4) is to allow the reaction product to react with an amine in aqueous solution (10% DMAE) to hydrolyze the ester into carboxyl group (see page 930, right col., 3rd paragraph). Tsugita teaches that for MALDI-MS, the matrix is a saturated solution of sinapinic acid or a-cyano-4-hydro-xycinamic acid in 0.1% TFA/acetonitrile (1:1 v/v) for dehydration (see page 930, right col. 1st paragraph). Therefore, Tsugita teaches using polar aprotic solvent for dehydration treatment in sub-step (5) before MADI-MS analysis.

In regard to Claim 25, Tsugita in view of Vogt teaches that the N-acylation protection process can be done by an alkanoic acid anhydride dissolved in a dipolar aprotic solvent. Tsugita also teaches using polar solvent for the subsequent reaction. (see page 930, right col. 3rd paragraph).

In regard to Claim 12, Tsugita does not specifically teach maintaining acetic anhydride in the sub-step (2). However, since the function of acetic anhydride is to form oxazolone at C-terminal for perfluoroalkanoic acid to act on in the sub-step (2), it would have be obvious to ordinary skill in the art to recognized that maintaining the concentration of acetic anhydride in the sub-step (2) may benefit the reaction.

In regard to Claims 26 and 27, Tsugita teaches that the method is developed both for proteins extracted from a polyacrylamide gel and for protein on an Immobilon-CD membrane, electroblotted from a protein spot on the gel (Page 931 left col., 2nd paragraph).

Response to Arguments

6. Applicant's arguments filed on 03/12/2009 have been fully considered but they are not persuasive.

The applicants argue that PFPMe and PFPA have different mechanism in the C-terminal peptide degradation reaction. Therefore, PFPMe can not be substituted by PFPA. PFPMe and PFPA have similar structure, and have been used in the same C-terminal peptide degradation process. Therefore, the substitute between PFPMe and PFPA is obvious.

The applicants argue that Tsugita by no means uses FAB-MS or MALDI-TOF-MS for the process disclosed in 2.13 C-terminal sequencing. Tsugita teaches using PFPA and using FAB-MS or MALDI-TOF-MS in the process disclosed in 3.1 multiple C-terminal sequencing. The ordinary skill in the art would recognize that the same method used in 3.1 multiple C-terminal sequencing can also be used in 2.13 C-terminal sequencing.

The applicants argue that Tsugita fails to teach or suggest any process in with chemical specific cleavage was carried out on the protein while maintained in a state of being bound on the polyacrylamide gel. The claims were rejected over Tsugita in view of Vogt. Vogt teaches a non-aqueous swelling system that carboxymethyl cellulose get treated with a dipolar aprotic solvent (N, N-dimethylacetamide with p-toluenesulfonic acid) yields a high reactive gel-suspension of he polymer.

The applicants argue that Vogt fails to teach or suggest any process for the preparation of a gel-suspension of CMC in the dipolar-aprotic solvent without p–toluenesulfonic acid. Vogt teaches that the dipolar–aprotic solvent can be used with other acid, although they may not swell CMC to a comparable extent. Tsguta'1992 used PFPA in C-terminal peptide degradation reaction. Therefore, ordinary skill in the art would recognize that dipolar-aprotic solvent with PFPA can also swell gels based Vogt's teaching.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT XU whose telephone number is (571)270-5560. The examiner can normally be reached on Mon-Thur 7:30am-5:00pm, Fri 7:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Kim can be reached on (571)272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

5/1/2009

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

RX